



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/597,328	01/10/2008	Abdul Waseh Basit	33327.001	9321

25005 7590 12/14/2011

Intellectual Property Dept.
Dewitt Ross & Stevens SC
2 East Mifflin Street
Suite 600
Madison, WI 53703-2865

EXAMINER

SHOMER, ISAAC

ART UNIT	PAPER NUMBER
----------	--------------

1612

NOTIFICATION DATE	DELIVERY MODE
-------------------	---------------

12/14/2011

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket-ip@dewittross.com

Office Action Summary	Application No. 10/597,328	Applicant(s) BASIT ET AL.	
	Examiner ISAAC SHOMER	Art Unit 1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 September 2011.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 5) ☒ Claim(s) 1,3-6,8,10-17 and 20-22 is/are pending in the application.
- 5a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 6) ☐ Claim(s) ____ is/are allowed.
- 7) ☒ Claim(s) 1,3-6,8,10-17 and 20-22 is/are rejected.
- 8) ☐ Claim(s) ____ is/are objected to.
- 9) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 12) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____. |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>14 September 2011</u> . | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

Applicants' arguments, filed 14 September 2011, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

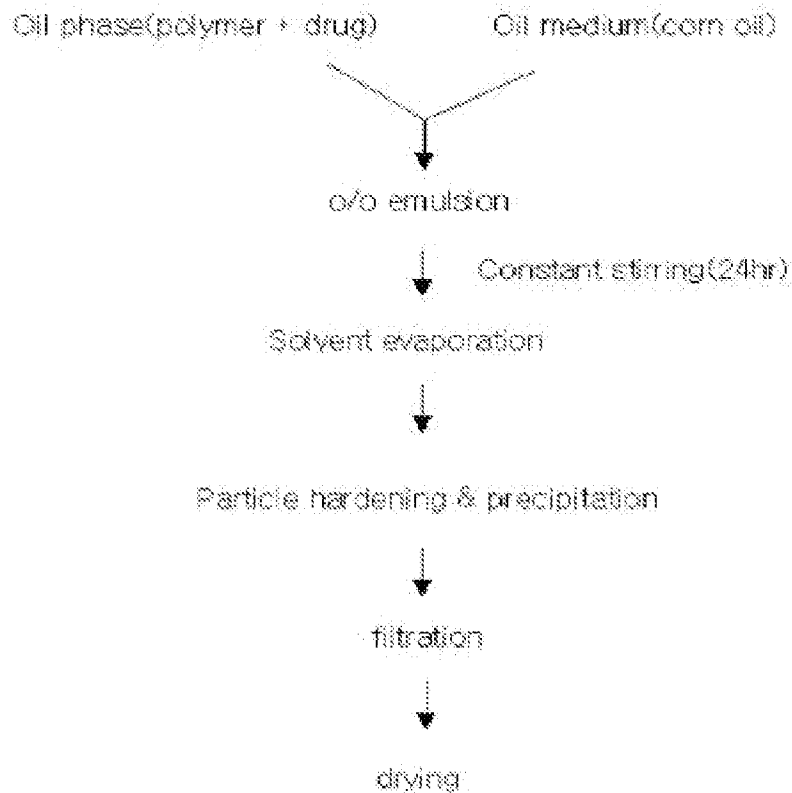
Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 3-6, 8, 10-13, 15, and 20 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. (Journal of Microencapsulation, 2002, Vol. 19, No. 6, pages 811-822) in view of Hassan (US 2002/0119916).

Kim et al. (hereafter referred to as Kim) teaches microspheres comprising the felodipine (a drug) which were prepared by an oil/oil emulsion evaporation method, as of Kim, page 811, abstract. In one embodiment, Eudragit RL and Eudragit RS (methacrylate copolymers as required by claims 1, 11, and 12) were dissolved in an acetonitrile/dichloromethane mixture then emulsified into corn oil using 2% Span 80 (polysorbate 80) as the surfactant, as of Kim, page 813, top two paragraphs, and page 1, Figure 1, reproduced below.

Art Unit: 1612



In the method of Kim, the particles made from said method are sized from 9.5 to 13.2 microns, as of Kim, page 811, abstract. Kim, when reviewing the prior art, teaches that systems comprising Eudragits are useful for the preparation dosage forms for oral administration, as of Kim, page 812, second full paragraph.

Kim does not teach "at least two surfactants", as required by claim 1.

Hassan is drawn to a process of manufacture of particles for the delivery of water insoluble drugs, as of Hassan, abstract, wherein said process is an emulsion process. Hassan utilizes surfactants which may have a HLB value from 1 to 20, as of Hassan, paragraph 0019. Hassan suggests polyoxyethylene sorbitan fatty acids generically, which are known by Hassan as "Spans," as of Hassan, paragraph 0027. Sorbitan sesquioleate is a preferred surfactant of Hassan, as of paragraph 0027, and the

Art Unit: 1612

surfactant known by the trade name Arlacel 83 is suggested, as of Hassan, paragraph 0038, wherein the term Arlacel 83 is a trade name for sorbitan sesquiolate. The particles made by the method of Hassan are taught for oral administration, as of Hassan, page 5 claim 21. Hassan teaches various drugs including prednisone, as of Hassan, paragraph 0012.

It would have been prima facie obvious for one of ordinary skill in the art to have substituted the surfactants of Hassan for those of Kim. This is because the surfactants of Hassan are predictably known to be useful in an emulsion for oral administration with a reasonable expectation of success, wherein oral delivery suggested by Kim. The simple substitution of one known element (sorbitan sesquiolate, of Hassan) for another (Span 80, of Kim), to achieve predictable results (making an emulsion for oral administration) is prima facie obvious. See MPEP 2143, Exemplary Rationale B. Furthermore, Hassan teaches the entire genus of surfactants known by the trade name "span" (which includes the surfactant Span 80 of Kim), yet teaches that sorbitan sesquiolate is preferred, as of Hassan, paragraph 0027, which would have provided the skilled artisan with even greater motivation to have used sorbitan sesquiolate.

Arlacel 83, as taught by Hassan, paragraph 0038, reads on the requirement of claim 1 of "at least two surfactants" as it is a combination of sorbitan monooleate and sorbitan dioleate, as of page 6 lines 6-7 of the instant specification. Furthermore, the term Arlacel 83 is also known as sorbitan sesquiolate, as of page 7 line 7 of the specification and Hassan, paragraph 0038.

As to claim 8, the above references do not specifically teach pH dependent release, as required by claim 8. However, the skilled artisan would have understood that the polymers used by Kim and Hassan, specifically the polymer known by the trade name Eudragit RS (as of Kim, abstract), would have possessed this property. The polymer known by the trade name "Eudragit RS" is recited by claim 11, and is disclosed by the specification at page 5 line 6. As such, the polymer known as Eudragit RS, which was used in the prior art, would have had the same properties.

Response to Arguments:

In applicant's arguments dated 14 September 2011, the following points are made.

1) Arguments against the prima facie case of obviousness:

A) Applicant argues that the skilled artisan would not have combined an element from the teachings of Kim with those of Hassan because Kim is drawn to oil-in-oil emulsions and Hassan is directed to oil-in-water or water-in-oil emulsions, and is silent with regard to oil-in-oil emulsions, as of applicant's arguments, page 7, first full paragraph.

This argument is not persuasive. Both Kim and Hassan relate to emulsions used to make drug delivery dosage forms for oral administration. As such, the skilled artisan would have understood that the surfactants taught by both Kim and Hassan would have been suitable for oral administration, as both types of surfactants are used in an oral dosage form. Furthermore, Hassan presents a long list of surfactants that may be used, as of Hassan, paragraphs 0019-0027. Included in the list is a teaching of the genus

Art Unit: 1612

known as "spans," as of paragraph 0027. As the surfactant taught by Kim is known by the name "span 80," the skilled artisan would have understood that the same surfactants useful for oil in water or water in oil emulsions, as taught by Hassan, would have also been predictably useful for oil in oil emulsions (as taught by Kim) with a reasonable expectation of success.

B) Applicant contends that it would not have been obvious to the skilled artisan to have substituted sorbitan sesquioleate, as of Hassan, for Span 80, as of Kim, because it would not have been obvious that sorbitan sesquioleate is capable of separating oil from oil, as required in an oil/oil emulsion, as of applicant's arguments, page 7, second and third paragraph.

This is not persuasive. The examiner disagrees that there would be significant differences in character between the oil/oil emulsion of Kim and an oil/water or water/oil emulsion as taught by Hassan. This is because the dispersed "oil" phase in the method of Kim utilizes acetonitrile, as of Kim, paragraph bridging pages 814 and 815, wherein the following is taught:

Acetonitrile is a unique organic solvent which is polar, water-miscible and oil-immiscible. All other polar organic solvents like methanol, ethyl alcohol, ethyl acetate, acetone, dimethylsulphoxide and tetrahydrofuran are oil-miscible and do not form emulsions of the polymer solution in oil (Viswanathan et al. 1999).

As such, in view of the fact that acetonitrile is miscible with water but not with oil, the skilled artisan would have expected that an emulsion phase comprising an acetonitrile phase would behave in a similar manner as an emulsion comprising a

Art Unit: 1612

water phase due to the miscibility of the two solvents, and the insolubility of acetonitrile in oil. As such, the skilled artisan would have been motivated to have used a solvent that can separate water from oil (as in Hassan) to have predictably separated acetonitrile from oil with a reasonable expectation of success.

C) Applicant disagrees that Hassan does not teach the genus of surfactants known by the trade name “span,” as of applicant’s arguments, paragraph bridging pages 7 and 8. Applicant further contends that Hassan does not identify the word “span” as a trade name.

This is not persuasive. The term “span” is identified as a polyoxyethylene sorbitan fatty acid ester, as of Hassan, paragraph 0027. While Hassan does not specifically state that the term “Span” is a trade name, the skilled artisan would have known that “span” is frequently used in the art as a trade name in the manner specified by Hassan. Furthermore, applicant does not provide an alternate hypothesis for Hassan's use of the term “Span.”

D) Applicant contends that the genus “polyoxyethylene sorbitan fatty acid esters” as taught by Hassan is a very large genus, as of applicant's arguments, page 8, first full paragraph. Applicant contends that the teaching of a genus does not render any Species within the genus as obvious.

This is not persuasive. This point is moot because Hassan teaches sorbitan sesquioleate, as of Hassan, paragraph 0027, which is the surfactant relied upon in the rejection. The fact that sorbitan sesquioleate is part of the genus known by the trade

name "Span" was mentioned to show the chemical similarities between the surfactants used by Hassan and by Kim.

2) Arguments regarding allegations of unexpected results:

Applicant contends that objective data from the present specification shows that Span 80 is not functionally equivalent to sorbitan sesquioleate in generating emulsions, as of applicant's arguments, page 8, second full paragraph, specifically pointing to page 12 lines 16-23 of the specification. Applicant contends that the use of Span 80 produced non-particulate lumps of polymer larger than 1 mm in diameter, whereas sorbitan sesquioleate produced spherical, non-aggregated, non-porous particles in the required size range.

Summary of Data: The specification presents one inventive example and multiple comparative examples. The inventive example uses sorbitan sesquioleate (known as Arlacel 83) as the surfactant system, as of page 12 Example 3, lines 16-23. Scanning electron microscopy (SEM) data show that these particles are non-aggregated, as of Figures 3A-3C. Other inventive examples include those presented on page 13, Examples 4 and 5. Figures 4A, 4B, and 5 appear to show that said particles are not aggregated.

The specification also presents comparative examples, wherein the following surfactants were used. In Example 1, Span 85 (as of page 11 Example 1), Span 65 (page 11 line 20), Span 80, Span 20, and Span 65 were tested. In example 2, Brij 52 and Brij 92 were tested. The data for these experiments is presented in Figures 1 and 2A-2E. Data for Span 80, Span 20, and Span 65 is not shown, apparently because

Art Unit: 1612

applicant was unable to advance the experimental testing regime to the point where SEM data could be taken.

Analysis: To establish unexpected results, the data presented by applicant must be statistically significant as well as practically significant. In this case, the skilled artisan would have recognized the practical significance of minimizing aggregation between microparticles.

To establish non-obviousness based upon unexpected results, it must be clear that the results would not have been expected by one of ordinary skill in the art. As evidence of the expectation of the skilled artisan, the examiner cites Haw ("The HLB System", Uniqema, 9 March 2004, 39 pages), (see last page for author information). Haw, 18th page, teaches that for mixing unlike oils together, surfactants with HLB values of 1-3 should be used. In this case, the successful examples shown by applicant use surfactants with a HLB of 3.7, which is outside the range specified by Uniqema for mixing unlike oils together.

Furthermore, applicant appears to have shown that surfactant systems with HLB values that are either greater or less than 3.7 both fail to produce the desired effect. As evidence, the examiner has presented ICI Americas Inc. ("The HLB System A Time-Saving Guide to Emulsifier Selection.", 22 pages, 8 chapters, Revised, March 1980) (hereafter referred to as ICI). ICI, pages 18-19, presents a table of the HLB values of various surfactants. ICI teaches that Span 20 and Span 80, both of which failed to produce non-aggregated particles in Example 1, have HLB values of about 9 and 4 respectively, both of which exceed the successful HLB value of 3.7. Likewise, Brij 52

Art Unit: 1612

and Brij 92, which failed in Example 2, have HLB values between about 4.5 and 5. As such, it appears that surfactants with HLB values that exceed the successful value of 3.7 fail to produce the desired effect.

Applicant also tested Span 65 in Example 1, which failed to produce the desired effect. This surfactant has a HLB value of less than 2. As such, applicant has tested one surfactant with a HLB value below the claimed value and found that this has failed.

Claim Scope: Applicant appears to have established that the use of a surfactant system with a HLB value of 3.7 unexpectedly is useful in making particles that do not aggregate. However, the unexpected results presented by applicant are not commensurate in scope with the claimed invention. Applicant recites a HLB range of 2-5 in claim 1, and applicant has not shown data for this range of HLB values. In fact, some of the failed comparative examples, specifically Span 80, Brij 52, and Brij 92 have HLB values in the range of 4-5, which is within the scope of the claimed invention.

Additionally, the examiner notes that Haw teaches that surfactants with HLB values of 1-3 are useful for oil/oil emulsions, as such, the range of 2-3, which overlaps with the claimed invention, would not have been considered unexpected.

Also, the examiner notes that claim 1 does not limit the solvent system. This appears to be crucial to the success of the surfactant system. As support for this position, the examiner cites page 11 lines 20-22 of the specification. This section of the specification explains the failure of Span 65 due to its failure to dissolve in liquid paraffin, as well as the acetone/methanol mixture. As the claim 1 does not limit the

Art Unit: 1612

solvent system to liquid paraffin or the solvent system to an acetone/methanol mixture, the claims are not commensurate in scope with applicant's showing.

Claim 16 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. (Journal of Microencapsulation, 2002, Vol. 19, No. 6, pages 811-822) in view of Hassan (US 2002/0119916) as applied to claims 1, 3-6, 8, 10-13, 15, and 20 above, and further in view of Satturwar et al. (Journal of Microencapsulation, Vol. 19, No. 4, 2002, pages 407-413).

In applicant's arguments, page 10, top paragraph, applicant contends that Satturwar does not address the shortcomings of Kim and Hassan. This is not persuasive, as there are no shortcomings to the teachings of Kim and Hassan regarding the rejection of claim 1. For this reason, the rejection of claim 16 is maintained.

Claims 1, 3, 4, 10, 14, 17, 21, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burnside et al. (US Patent 5,824,638) in view of Pather et al. (US 2003/0077306 A1).

Burnside et al. (hereafter referred to as Burnside) is drawn to a pharmaceutical composition for oral insulin delivery and a method of making said composition, as of Burnside, title and abstract. Said composition is made by a water-in-oil emulsion process, including a discontinuous hydrophilic phase and an aqueous hydrophobic phase, along with surfactants, as of Burnside, column 16, claim 1. Said hydrophilic phase may include ethanol, as of Burnside, column 13 Example 13, which teaches the

Art Unit: 1612

use of Hank's buffer with ethanol, as of Burnside, column 13 lines 44-46. Inclusion of polymers such as cellulose derivatives and methacrylic acid derivatives known by the trade name "Eudragit" is taught as of Burnside, column 6 lines 19-29. Manufacture of particles that are 100 microns in size or less are taught as of Burnside, column 2 line 51.

Burnside also does not teach a surfactant system with the required HLB.

Pather et al. (hereafter referred to as Pather) teaches that w/o emulsions (water-in-oil emulsions) require low HLB emulsifying agents, with HLB values of approximately 1 to 7, as of Pather, paragraph 0036.

It would have been prima facie obvious for one of ordinary skill in the art to have used a surfactant system that ranges from 1-7, as taught by Pather, in the process of Burnside. This is because Pather teaches that a surfactant system in this range is useful for water-in-oil emulsions. As Burnside is drawn to a water-in-oil emulsion, the skilled artisan would have been motivated to have used a surfactant system with a HLB value in this range to have predictably stabilized the emulsion of Burnside with a reasonable expectation of success. Furthermore, the skilled artisan would have been motivated to have used at least two surfactants in view of the teaching of Burnside, column 3 lines 55-57, which teaches the presence of a surfactant and a cosurfactant, indicating that at least two surfactants may be present.

As to claims 3 and 4, Pather teaches a HLB range from 1 to 7, which overlaps with the HLB ranges of 3 to 4 of claim 4. While the prior art does not disclose the exact claimed values, but does overlap: in such instances even a slight overlap in range

Art Unit: 1612

establishes a *prima facie* case of obviousness. In re Peterson, 65 USPQ2d 1379, 1382 (Fed. Cir. 2003).

As to claim 10, Burnside teaches the methacrylate polymer Eudragit as of column 6 lines 19-29.

As to claims 14 and 21, Burnside teaches the incorporation of ethanol in the aqueous phase, as of Burnside, column 13 Example 13. As such, ethanol is a component of the solvent of the dispersed phase. This reads on the solvent requirement of claims 14 and 20.

As to claim 17, Burnside teaches the method for preparation of the composition, as of Burnside, column 7, last paragraph. This method does not appear to teach the use of heating or cooling, and as such, it is understood that the preparation occurs at room temperature, reading on the temperature requirement of claim 17.

As to the particle size requirement of claim 22, Burnside teaches manufacture of particles that are 100 microns in size or less as of Burnside, column 2 line 51. This overlaps with the required size range of 30 to 100 microns.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 8:00 AM - 5:00 PM Monday-Friday.

Art Unit: 1612

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ISAAC SHOMER/
Examiner, Art Unit 1612

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612